1

DESCRIPTION

Method and Apparatus for Closed Loop Drug Delivery

Cross-Reference to Related Applications

This application is related to U.S. Serial No. 308,683, filed February 9, 1989, which is a continuation-in-part of U.S. Serial No. 157,875, filed February 19,
5   1988, the disclosures of which are incorporated herein by reference.

Field of the Invention

The invention relates generally to a closed loop drug delivery system using a rule based administration method.
10 More particularly, the invention relates to methods and apparatus for use in the administration of an exercise simulating agent ("ESA") which elicits a cardiovascular response similar to that resulting from aerobic activity. This apparatus and method is used advantageously in the
15 diagnosis, evaluation and treatment of coronary artery disease, by providing for closed loop drug delivery to generate a cardiac stress related response.

Background and Introduction to the Invention

Heart disease is the number one killer in the United
20 States and a leading cause of death worldwide. Currently, heart disease, stroke and related disorders account for nearly one million deaths per year in the United States, almost as many deaths as from all other causes combined. Cardiovascular and cerebrovascular diseases affects
25 approximately 65 million people in the United States, roughly one out of every four. Approximately 5 million people in the United States suffer from coronary artery disease ("CAD"), resulting in over 1.5 million heart attacks yearly, of which over 500,000 are fatal. The
30 annual economic cost of cardiovascular disease alone is estimated to be 85 billion dollars.

2

Atherosclerosis is the most common form of arteriosclerosis, commonly referred to as 'hardening of the arteries'. Atherosclerosis is a degenerative process that narrows or blocks arteries in the heart, brain and
5   other parts of the body. The interior walls become lined with deposits of fat, cholesterol, fibrin, cellular waste products and calcium. These deposits form a rough, thick surface inside the blood vessels and interfere with both the smooth flow of blood and the amount of blood carried
10   through the arteries. This narrowing of the blood vessels restricts blood flow, causing ischemia (deficiency of blood at the heart tissue due to either functional con-strictions or obstructions of a blood vessel), and is the underlying pathologic condition in many forms of cardio-
15   vascular disease including CAD, aortic aneurysm, peripheral vascular disease and stroke.

In the majority of cases, the first indication of atherosclerosis is seen during exercise when the oxygen requirement of the heart muscle (myocardium) increases.
20   Indeed, atherosclerosis is generally silent until it manifests itself as CAD, peripheral vascular disease, stroke or sudden death.

Disorders of the coronary arteries are common manifestations of atherosclerosis. CAD develops when the
25   coronary circulation is insufficient to supply the oxygen requirements of the heart muscle, resulting in ischemia. CAD has three major clinical manifestations: angina pectoris, a condition marked by periodic episodes of chest pain, especially during exertion, that result from tran-
30   sient and reversible myocardial ischemia (when CAD has progressed such that it is clinically apparent, it is also referred to as ischemic heart disease); myocardial infarc-tion, the term used to describe acute necrotic changes in the myocardium that are usually secondary to coronary
35   occlusion (heart attacks); and sudden death, an unexpected cardiac death occurring within an hour of the onset of the heart attack, often without symptoms.

3

Diagnosis and evaluation of coronary artery disease
is challenging to the practicing physician because myo-
cardial ischemia occurs at irregular intervals or without
pain or other symptoms. Historically, the diagnosis and
5   management of coronary artery disease has been performed
using both non-invasive and invasive procedures. Prior to
1970, the principal non-invasive techniques available for
the evaluation of the patient with heart disease were a
clinical examination, chest x-ray and electrocardiograph
10   ("ECG"). If these various modalities were inadequate and
clinical symptoms were present, patients were often
subject to invasive techniques of cardiac catheterization,
selective angiography, or both, with the resultant discom-
fort, risk and necessity for hospitalization.   More
15   recently, the most common non-invasive diagnostic proce-
dure is the resting ECG. An ECG is performed with the
patient at rest, and is useful for diagnosing cardio-
vascular disease states such arrhythmias, hypertrophy
(enlargement of the heart), and evidence of an evolving or
20   prior heart attack. However, this test is generally not
sufficiently sensitive to detect coronary disease in its
early stages. More recently, echocardiography and radio-
nuclide imaging have been used for non-invasive diagnostic
purposes. Echocardiography employs ultrasound to create
25   an image of the heart, producing real time images of
anatomical structures and heart wall motion. Radionuclide
imaging uses radioactive agents and specialized camera
equipment to create an image of the heart. Once injected
into the blood stream, radionuclide imaging agents such as
30   thallium are taken up rapidly by healthy cardiac tissue,
while poorly profused tissues take up less of the tracer.
Areas with less of the imaging agent indicate the presence
of occluded coronary arteries or dead tissue.
While each of the primary noninvasive diagnostic
35   techniques of ECG, echocardiography and radionuclide
imaging may be performed with the patient at rest, their
diagnostic value is enhanced by stressing the patients

4

heart. Exercise increases the heart's need for oxygen, causing healthy coronary arteries to become dilated and blood flow through these vessels to increase. Occluded arteries impede blood flow and may not accommodate the

5   increased needs of the heart, causing ischemia. Ischemia may elicit a symptomatic response, e.g., chest pain, or may cause cardiac disfunction, e.g., abnormal heart wall motion, which can often be diagnosed by these non-invasive methods.

10   Currently, the most common exercise stress testing is performed with ECG monitoring. Typically, exercise stress testing is performed after a baseline resting ECG is taken. A patient is then closely monitored through a protocol of sequential levels of exercise. The Bruce

15 protocol is the most common protocol used in the United States. It specifies the speed and level of the incline of a motor driven tread mill during a total of seven 3-minute exercise states with no rest periods. The test is stopped when any of the following occur: when the

20 protocol is completed; when the patient reaches a pre-set heart rate goal; when the patient experiences acute discomfort; when a diagnostic change occurs in the ECG or blood pressure; or when the patient fatigues.

    Despite the fact that exercise stress testing is an

25 important method for the diagnosis of coronary artery disease, there are numerous drawbacks which limit its overall usage. A significant problem with the procedure is that exercise must be maximal in order to obtain the greatest sensitivity. In other words, for a test to be

30 considered diagnostically revealing, either the patient must reach a level of stress that causes ischemia or the patient must complete the protocol by reaching a predetermined maximal heart rate.

    The first group of patients with whom exercise stress

35 testing cannot be used are those who are physically unable to exercise. Approximately 20 - 30% of the relevant subject population fall in this category. Often, patients

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cannot exercise due to any number of causes, such as, arthritis, limb abnormalities, obesity, obstructive lung disease, peripheral vascular disease or other disfunction.

The second major class of patients incompatible with exercise stress testing are those for whom the results are inconclusive due to an inability to achieve the necessary heart rate. Again, this comprises from 20 - 30% of the subject patients.

Thirdly, exercise stress testing involving physical motion is generally incompatible with echocardiography and radionuclide imaging. With echocardiography, lung expansion and patient movement reduces the quality of the echocardiography ultrasound image. With radionuclide imaging, the image cannot be made at the moment of peak stress when diagnostic capability is greatest. Generally, the physical motion of the body caused by exercise generated stress diminishes the image quality or requires a time lapse resulting in suboptimal diagnosis.

Fourthly, exercise stress testing by physical motion is generally inconvenient to both patient and doctor. For example, a maximal stress test exhausts most patients and involves a significant recovery time. Additionally, maximal stress tests involve a degree of risks for the patient of falling which is directly related to the use of a tread mill. Because of the physical movement associated with the exercise, placement of the electrodes is also a problem. Specially designed electrodes which minimize motion artifacts must be securely attached. Finally, placing the electrodes can involve shaving the chest for a man, and sometimes burnishing the skin to achieve appropriate electrode contact.

Taken as a whole, these drawbacks make exercise stress testing an inconvenient test for both patient and physician. Because of its inherent difficulty, lack of sensitivity, lack of specificity, and cost, exercise stress testing is not generally recommended for asymptomatic individuals.

6

It is desirable to perform diagnosis for coronary artery disease by methods which can stress the heart in a manner which mimics aerobic activity while not forcing the patient to actually engage in strenuous physical activi-

5   ties. A test wherein the heart is stressed without the need for physical exercise would be not only of great practicality, but would also allow for the testing of individuals who heretofore have been unable to engage in exercise stress testing.

10 Various drugs exist which elicit acute and adaptive cardiovascular responses similar to the types of responses elicited by aerobic activity. They will be referred to as Exercise Simulating Agent beta agonists or "ESA™ Beta Agonists" for purposes of this invention. Generally,

15 these drugs are catecholamines. Catecholamines are essential compounds in the body and play many important roles. For example, adrenaline and noradrenaline are natural catecholamines which act as neurotransmitters and hormones, controlling among other things, the function of

20 the heart muscle. During physical exercise for an exercise stress test, adrenaline and noradrenaline are released, increasing the rate and force of contraction of the heart and blood pressure. These natural catecholamines do not act selectively on the heart, however, and

25 have side effects which make them unsuitable as agents to pharmacologically stress the heart.

Several groups have described the intravenous infusion of synthetic catecholamines. In one example, United States Patent No. 3,987,200 entitled "Method for

30 Increasing Cardiac Contractility" issued to Tuttle et al. on October 19, 1976, discloses a synthetic catecholamine dobutamine. Dobutamine elicits certain specific cardiac responses without the adverse side effects that would accompany administration of a natural catecholamine.

35 Dobutamine exerts a positive inotropic effect (increasing heart contractility) without inducing arrhythmia and with minimal heart rate and blood pressure effects. When

7

infused intravenously at high doses, dobutamine elicits
increases in heart rate, myocardial contractility,
arterial blood pressure, and coronary and skeletal muscle
blood flow. Such responses resemble the effects of
5   physical exercise. Although the heart rate does increase
with infusion of dobutamine, the drug was designed to
specifically minimize this effect. Increasing heart rate
is referred to as positive chronotropic effect.
    More recently, the novel catecholamine analogue,
10   arbutamine, has been developed. Arbutamine appears to act
selectively on the heart and cause an increase in the rate
and force of contraction of the heart and blood pressure.
Arbutamine is described in detail in Tuttle et al.
"Diagnosis, Evaluation and Treatment of Coronary Artery
15   Disease by Exercise Simulation Using Closed Drug Delivery
of an Exercise Simulating Agent Beta Agonist", Serial
Number 308,683, incorporated by reference, above.
Arbutamine is a catecholamine analog designed to stress
the heart pharmacologically. Arbutamine produces a dose-
20   dependent cardiovascular response similar to that of
physical exercise. Accordingly, the heart rate can be
increased incrementally by gradually increasing the amount
of drug administered. Generally, the duration of action
of arbutamine is short, and when drug delivery is termi-
25   nated, the heart returns to a normal range of activity
within a period of time similar to that which occurs after
physical exercise. Tuttle et al. contemplate a closed
loop drug delivery system in which the response variable
(e.g., heart rate) is monitored for effect caused by the
30   input variable (e.g., drug infusion rate). Computer
control of the closed loop drug delivery is contemplated.
The drug delivery device administers arbutamine to the
patient, monitors the patients heart rate and optionally
blood pressure, and controls the rate of drug delivery to
35   obtain the desired heart rate. This system is advantage-
ously useful in connection with widely used cardiac

8

testing procedures, such as ECG, echocardiography and radionuclide imaging.

   Ordinarily, drug delivery systems are control systems having an input-response relationship. A drug input, such
5 as an absolute amount or an infusion rate, produces a physiological response related to the input. Typically, the input (such as drug infusion rate) is used to control some parameter associated with the response variable, such as a desired rate (heart rate, blood pressure level,
10 etc.).

   Broadly speaking, drug delivery systems are either open loop delivery systems or closed loop delivery systems. An open loop drug delivery system is one in which the drug is delivered at a predetermined rate
15 without any direct or automatic adjustment in response to physiological response variables. A closed loop drug delivery system is one in which a drug is delivered in automatic response to feedback of a physical signal or response, which could include responses such as heart
20 rate, blood pressure, ECG parameters, heart output or other similar physical response. While numerous types of closed loop systems exist, representative categories of control schemes include: linear-nonlinear, deterministic-stochastic, and adaptive-nonadaptive. More particularly,
25 closed loop delivery systems include predictive type and proportional-integral systems. In a predictive system, the input quantity is correlated to the difference between the current value of the response variable and the desired or target level (i.e., error term). The proportional-
30 integral systems utilize a proportionality error term plus an integral error term, each having different contribu-tions to the overall input amount.

   Closed loop drug delivery systems have been used for therapeutic purposes to maintain a physiologic parameter.
35 One specific example is the use of a closed loop drug delivery system to control infusion of Nipride to control a patient's blood pressure. Such a system is described in

9

Petre et al., "Infusion Pump Control", United States
Patent No. 4,392,849. Such a system is designed to main-
tain stability of a physiological parameter, as opposed to
variation of that parameter for diagnostic purposes. Yet
5   further examples of closed-loop drug delivery systems for
therapeutic purposes are disclosed in Newman, PCT
Application WO 88/08729, entitled "Iontophoresis Drug
Delivery System", published November 17, 1988. Various
therapeutic closed-loop drug delivery applications are
10 mentioned, including for medication delivery, control of
blood pressure, insulin delivery and administration of
pain killing drugs.

There are many unique and important obstacles
presented in effective diagnosis utilizing a closed loop
15 drug delivery system, especially for diagnosis of the
heart. For example, there is potentially a long time
delay for arrival of the drug at the target organ, that
being the time between the administration at an intra-
venous or transdermal location and arrival at the heart.
20 Secondly, it is quite often the case that various patients
respond differently to a given drug, making response
predictability more difficult. Third, there is the
possibility of excessive build up of a drug in a patient.
Fourth, safety monitoring for a contra-response must be
25 done, and drug delivery terminated. Finally, monitoring
the heart rate is a difficult signal to track as the heart
rate is a very noisy signal.

Despite the clear desirability of a system which is
effective in the diagnosis and management of CAD, no
30 effective system has been known heretofore.

Summary of the Invention

A closed loop drug delivery system uses patient
response and rule based decision making methods to achieve
operator specified responses for diagnostic purposes. In
35 the preferred embodiment, the system causes stress thus
allowing cardiac diagnosis by administration of an exer-

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cise simulating agent drug to pharmacologically stress the
heart. The physiological response may be monitored by any
known method, including ECG, echocardiography and radio-
nuclide imaging. An acute cardiovascular response is
5   achieved like that induced by physical exercise. Specifi-
cally, the results include increased heart rate, increased
cardiac contractility and increased systolic blood pres-
sure levels. As a result, increasing the heart's demand
for blood and oxygen helps reveal diseased arteries which
10 cannot supply the blood to the heart.

The overall drug delivery device consists of a
hardware system and an expert, rule based, control system.

The hardware system acquires various physiological
parameters of the patient and further receives operator
15 specified information and based upon the inputs, outputs
the desired rate of ESA drug infusion. In the preferred
embodiment the physiological parameters are the heart rate
and blood pressure, and the operator specified information
is a protocol. A microprocessor based hardware system is
20 used. While one or more processors may be used, in the
preferred embodiment a data acquisition processor func-
tions principally to receive and distribute the patient's
physiological response information, a display control
processor functions principally to display information and
25 to receive user specified information, and a drug delivery
processor functions principally to determine the drug
delivery rate. The drug delivery processor controls a
drug delivery source, such as an intravenous infusion pump
or transdermal iontophoretic delivery system. Optionally,
30 various displays may provide information to the operator,
with both hard key and soft key inputs available.

The method generally consists of determining the ESA
drug infusion rate by reference to various rules for
various modes, such as RAMP, HOLD, TARGET, and LEVEL, and
35 transitions between modes, such as transitioning from RAMP
to HOLD, based on measured physiologic values, such as
heart rate.

11

More particularly, the method generally comprises the following steps:

Determining the individual patient response to the drug, such as onset delay for a particular patient. Patient specific information is used in conjunction with the rule based decision making. In the preferred embodiment, an initial open loop administration of a bolus of drug based on the patient's weight generates physiologic response data from which patient dose response parameters are determined.

The user specifies the particular heart rate protocol desired. A simple protocol would consist of setting a desired maximum heart rate and the desired rate of increase in heart rate. The user may specify any desired order or combination of heart rate targets. The user additionally specifies patient specific information, such as a patient's age and weight.

During the drug delivery phase, the ESA drug is administered to cause a physiologic response. When in the RAMP mode, the rate of increase in heart rate is more important than the actual difference between the target heart rate and the present heart rate. When the heart rate is approaching the target heart rate maximum, the drug delivery is modified to achieve the heart rate target with a minimum of overshoot. In the preferred embodiment, the amount of ESA drug is reduced or eliminated prior to reaching the target heart rate maximum.

Optionally, the user may enter the HOLD mode at any time. The HOLD mode seeks to maintain the heart rate at the level existing at the time the HOLD was initiated. Preferably, the HOLD heart rate is achieved with minimum overshoot. In the preferred embodiment, when a HOLD is called, the infusion rate is dropped, followed by resumption of infusion to a rate necessary to sustain the desired heart rate.

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In one aspect of this invention, a protocol compris-
ing at least a target heart rate and a plan to achieve the
heart rate are defined prior to the drug phase, and the
protocol may be modified after the drug phase has begun.
5 In this way the operator may vary the protocol during the
test so as to maximize the diagnostic results.

In another important aspect of this invention, a
protocol is defined which includes a target value, a plan
to achieve the target value and an acceptable zone of
10 deviation from the plan. During the drug phase, should
the patient physiological variable, such as heart rate,
fall outside the acceptable zone of deviation from the
plan, alternate rules are followed.

In another aspect of this invention, the measured
15 physiologic parameter is filtered prior to use in the
control method. In the preferred embodiment, the heart
rate measured, such as by an ECG, is sent through a low
pass filter to enhance performance of the control system.
More particularly, a filter with an exponential forgetting
20 factor is used along with clipping of outliers, which
enhances the signal and reduces the response of the drug
administration method to noise.

In yet another aspect of this invention, various
alerts and alarms are used to warn of potential hazardous
25 conditions, or to terminate drug administration in the
event of a hazard. Advantageously, the alerts and alarms
include such conditions as: a sudden change in a physio-
logic variable, such as blood pressure or heart rate, the
condition where each or a combination of the heart rate
30 and blood pressure are in a marginal condition or
excessive heart rate.

Optionally, user oriented interfaces are provided for
ease of operation. In the preferred embodiment, a display
system provides data on patient condition and response, as
35 well as an indication of the user specified protocol
information. A soft key system is useable with the
display to provide for flexible user input.

13

In summary, the various modes of RAMP, LEVEL, TARGET, and HOLD, and the transitions between any of them, such as RAMP to HOLD, are controlled by a rule based, expert system based upon action of the hardware to achieve the

5   desired physiological response. A protocol may be changed by the operator even after drug delivery has begun. Further, the control system itself will change administration rules if a patient response deviates from an acceptable zone.

10   Accordingly, it is a principal object of this invention to provide for improved diagnosis, prognosis and management of coronary artery disease.

It is yet a further object of this invention to provide for effective physiological stress of a patient

15   without physical exertion of a patient.

It is an object of this invention to permit stress testing of patients who could not otherwise be tested due to an inability to exercise.

It is yet a further object of this invention to

20   permit enhanced echocardiography and radionuclide imaging of patients under stress condition.

It is yet a further object of this invention to enhance patient safety, such as by reducing overall drug dosage.

25   It is yet a further object of this invention to provide a HOLD mode which achieves the desired heart rate with a minimum of overshoot, which enhances safety by not requiring a restart, thereby reducing total drug dosage, and which reduces the total testing time.

30   It is yet a further object of this invention to provide various alerts and alarms to enhance patient safety.

Brief Description of the Drawings

Fig. 1 is a block diagram of the overall control

35   system.

Fig. 2 is a perspective view of the ESA device.

14

Fig. 3 is a graph of heart rate versus time showing various control modes.

Fig. 4 is a block diagram of the HR input filter system.

Fig. 5 shows heart rate response and infusion rate for a constant infusion of drug as a function of time.

Fig. 6 shows the heart rate and drug delivery rate as a function of time for a protocol of a RAMP to a heart rate target.

Fig. 7 shows the heart rate and drug delivery rate as a function of time for a protocol of a RAMP to a first heart rate target followed by a RAMP to a second heart rate target.

Fig. 8 shows the heart rate and drug delivery rate as a function of time for a protocol of a RAMP to a heart rate target, including a HOLD.

Fig. 9 shows the heart rate and drug delivery rate as a function of time for a protocol which revealed ischemia.

Fig. 10 is a block diagram of the hardware system.

Detailed Description of the Invention

Overview of the System and Method

Fig. 1 shows a block diagram of the ESA system 10. The ESA device 10 receives operator inputs 12, including the operator specified protocol (such as heart rate slope, heart rate hold and target heart rate) and patient information such as weight, age and gender. The ESA device 10 additionally receives physiological parameter inputs 14, such as heart rate and optionally blood pressure of the patient 15. The ESA device 10 provides various forms of outputs, including display outputs which provide information to the operator. The ESA device 10 outputs the drug 16 infusion rate or the drug itself if the drug delivery mechanism is included within the ESA device 10. Finally, the ESA device 10 outputs various alerts and

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alarms to warn the user of specified conditions or to
terminate drug administration.

The physiological input of measured heart rate 14
when input to the ESA device 10 goes through a heart rate
5   filter to produce an average heart rate (HRa). At this
time the alerts and alarms for irregular heart rate and
unstable heart rate may be activated if appropriate. The
operator inputs 12 are provided to the control system, and
include the input of MODE selection. The operator input
10   12 also includes the desired heart rate target which,
during operation, is utilized in conjunction with the
computed average heart rate to generate an input to the
control system. The alert for no start up differential
heart rate is derived from the heart rate average and MODE
15   selection. Additionally, the average heart rate is used
for saturation detection, and the associated alert or
alarm for saturation, slope estimation and patient gain
estimation. These in turn are provided to the control
system as inputs. Based upon these inputs to the control
20   system, the output of the control system is used to
control the infusion 16. An alert or alarm for maximum
dose utilizes the output from the control system. The
maximum dose rate and the maximum total dose may be
monitored as desired.
25   Fig. 2 shows a perspective view of one design for the
ESA device. A housing 20 generally includes a monitoring
system, drug delivery controls and a drug delivery mech-
anism. In the preferred embodiment the monitoring system
includes a screen 22 for display of information for the
30   operator, system status lights 24 and soft keys 26. The
display 22 is conventionally used to display an indication
of the function of the soft keys 26. The drug delivery
controls include various hard keys 28, which optionally
include LEDs within them. The hard keys 28 may be used to
35   enter, by way of example, the heart rate protocol (such as
heart rate target, heart rate slope, or HOLD heart rate),
numerical data such as a patient's age, or may cause other

16

actions such as alert and alarm silence. The drug delivery mechanism may consist of any known form, whether intravenous or transdermal drug delivery. In the preferred embodiment, an IV pump 30 drives a syringe 32 to
5   deliver the ESA drug via an intravenous (IV) administration set and catheter 34. The housing contains various functional elements such as an on/off switch 36 and an AC power receptacle 38. Optionally, a data transfer port, such as an RS-232 connector 40, is included. ECG leads
10 and non-invasive blood pressure cuff 44 are attached through the housing 20.

        The drug administration method may be broadly classified into three time periods -- predrug, drug and postdrug. Fig. 3 shows a plot of heart rate versus time.
15 The predrug, drug and postdrug periods are labelled above the graph.

        The predrug time period is considered to be from when the monitoring leads 42 are attached (in the case of ECG monitoring) to start of drug administration. During this
20 time a patient's baseline is established, principally for resting heart rate and blood pressure. During this period, the operator may enter patient related information such as age, weight and gender on the hard key pad 28. Further, the operator would specify the protocol, typic-
25 ally consisting of at least a heart rate target (e.g., 60 beats per minute over baseline) and the desired heart rate slope (e.g., increase of 8 beats per minute). Finally, during the predrug period the operator would typically prepare the drug syringe 32 and IV administration set and
30 catheter 34, or if a transdermal delivery system is used, prepare the drug delivery electrodes.

        In Fig. 3, the baseline heart rate is shown prior to the time T0 and the heart rate target is labelled on the y-axis and marked with a horizontal dotted line.

35   The drug phase begins with the initial administration of drug and ends when drug administration is stopped. An initial bolus of drug is provided to the patient, and

17

the patient response in heart rate monitored. During the
drug phase, various operational modes exist. Among these
modes are the LEVEL mode, the RAMP mode, the TARGET mode
and the HOLD mode. Fig. 3 shows the LEVEL mode from time
5   T1 to T2 and from T7 to T8, the RAMP mode from times T2 to
T3, T4 to T5 and T8 to T9, the TARGET mode from T5 to T6,
and the HOLD mode from time T3 to T4. The LEVEL mode
occurs early in the drug cycle and is characterized by a
generally uniform heart rate. The RAMP mode occurs during
10   the drug phase and is characterized by a rate of increase
in heart rate. The TARGET mode occurs during the drug
phase and is characterized by a decreasing rate of heart
rate increase. The HOLD mode occurs during the drug phase
and is characterized by a relatively uniform heart rate.
15   In addition to the various operational modes themselves,
there are transitions from mode to mode such as from RAMP
to HOLD. The drug phase is exited when the operator
issues a stop or interrupt, or an alarm is generated by
the ESA device, or the heart rate target is achieved.
20   The postdrug phase begins when drug administration
ends. During this period, the heart rate and blood pres-
sure of the patient are monitored. As shown in Fig. 3,
the heart rate in the postdrug phase, T6 to T7 and after
T9, decreases after drug administration ceases, in a
25   manner not unlike heart rate response following termina-
tion of exercise.
        As shown in Fig. 3, protocols may go from a postdrug
phase to a further drug phase, shown at the transition
time T7.

30   Filtering of the Measured Physiologic Parameter
        The ESA device 10 receives the heart rate signal from
a source, such as an ECG monitor. The measured heart rate
can be a very erratic signal. Because of the large vari-
ability in the heart rate signal, a low pass filter is
35   preferably used to extract the slower dynamics correspond-
ing to the response of the heart rate to drug infusion.

18

Additionally, since the heart rate serves as the feedback
signal to the control system, large or frequent outliers,
that is signals falling outside an expected window around
the heart rate, would introduce undesired fluctuations in
5 the infusion rate profile. On the otherhand, excessive
averaging would distort the heart rate signal and present
an incorrect patient profile to the control system.

Fig. 4 shows a block diagram of the basic filtering
method of the preferred embodiment. The measured heart
10 rate HR(k) 50 represents the unfiltered signal as supplied
from the patient monitoring device. The unfiltered heart
rate signal HR(k) has the outliers removed 52 prior to
averaging. The output of the filter circuit is the
filtered average heart rate HRa(k) 54. In the preferred
15 embodiment, the average heart rate HRa(k) 54 is derived
from an averaged signal having an exponential forgetting
factor. A fraction G is summed with a fraction 1 minus G
of the preceding averaged heart rate signal HRa(k-1) 56.
Typically, sampling is done every 5 seconds.

20 In the preferred embodiment, the following method and
parameters have proved useful for filtering the heart rate
to enhance operation of the drug administration control.
To obtain the heart rate from the peak to peak interval
(called "rr") measurement from the ECG signal, the
25 following calculation is performed:

$$\overline{rr}(t+1) \; = \; \frac{7}{8} \; * \; \overline{rr}(t) \; + \; \frac{1}{8} \; * \; rr(t+1) \qquad (1).$$

The heart rate at time t is given by:

$$HR(t) \; = \; \frac{60}{\overline{rr}(t)} \qquad\qquad (2).$$

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The heart rate value is updated every time a new R-wave is
detected. The control system samples this HR signal every
5 seconds to acquire a new value for feedback control.

The following heart rate filtering rules were
35 discovered based on actual test data, and generally
provide for outlier clipping where a measured signal is
either more than 6 beats per minute above or 8 beats per

19

minute below the average heart rate. The following rules
have proved effective in successfully filtering input
heart rate.

$$HRdiff(t+1) = HR(t+1) - HRa(t) \quad [-8 < HRdiff < 6] \quad (3)$$

$$G(t+1) = (G(t)/(1 + G(t))) + 0.04;$$

$$\hspace{10cm} (4)$$

$$G(0) = 1$$

$$HRa(t+1) = HRa(t) + (G(t+1) * HRdiff(t+1));$$

$$\hspace{10cm} (5)$$

$$HRa(0) = HR(0)$$

Establishing a Baseline Heart Rate

During the predrug phase, the baseline heart rate is
established. The baseline heart rate is defined as the
average heart rate at the initial start of drug delivery.
Fig. 3 shows the baseline heart rate as the heart rate on
the y-axis prior to the time T0. In the preferred embodi-
ment, the control method determined heart rate changes
relative to the baseline heart rate. Accordingly, it is
important that an accurate baseline heart rate is
established.

There are several conditions which indicate that a
patient's heart rate has not reached a baseline or that
the control system does not have sufficient data from
which to calculate the baseline heart rate. In either of
these cases, a nonacceptable condition or value (such as
a heart rate of zero (0)) is returned as the baseline
heart rate, indicating that drug initiation must be
delayed until a valid baseline heart rate has been estab-
lished. In the preferred embodiment, any of the following
conditions will prevent the baseline heart rate from being
established:

(1) Receiving less than two minutes (24 samples) of
valid ECG measurements.

(2) Presence of an excessively low heart rate, e.g.,
heart rate less than 26 bpm, or excessively high heart

rate, e.g., heart rate more than 120 bpm, while the baseline is being established.

(3) An ECG lead coming loose, the baseline heart rate being reset to a nonacceptable condition or value
5 (e.g. zero heart rate) for half a minute.

(4) The existence of an "irregular heart rate" condition, which is defined to be an absolute (positive or negative) difference of more than 20 bpm between the measured heart rate and the averaged heart rate (HRa) for
10 2 consecutive samples.

(5) The presence of excessive noise in the measured heart rate signal, which in the preferred embodiment is measured as the variance (or sum of the square of the error between the measured heart rate around the current
15 running average HRa). The variance is estimated using the following formula:

$$smsq(t+1) = smsq(t) + (c * ((HR(t)-HRa(t))^2 - smsq(t)))$$

$$(6).$$

where $smsq(0) = 20$; and $c = 0.1$
20 Excessive noise may indicate a problem with the ECG leads or the R-wave detection. The constant "c" determines the rate at which the estimated sum of the squares will be updated with information from newly acquired data. In the preferred embodiment, the estimate of the noise variance
25 is not updated if any of the following conditions exists: (1) an irregular heart rate condition is detected, (2) the ECG leads are off, or (3) an uninterpretable heart rate, that is, excessively low or high heart rate, is observed. If the estimate of the noise variance exceeds 100 bpm^2, the
30 baseline heart rate is set to a nonacceptable condition or value (e.g. zero heart rate). Optionally, if the estimate of the noise variance exceeds 200 bpm^2, an alarm is sounded.

The Drug Phase
35   Once a valid baseline heart rate is established and the other pre-drug phase requirements satisfied (such as

setting of protocol and establishing the drug-delivery
system), the drug phase may be entered.

Drug Response

        Fig. 5 shows a typical response curve of the heart
5   rate to constant infusion of arbutamine, the ESA drug.
The change in heart rate from the baseline value is shown
on the y-axis on the left, and the drug infusion rate
(μg/kg/min) is shown on the right hand y-axis.   Drug
infusion incurred at approximately time 350 and ends at
10 approximately time 715, with a constant infusion rate of
0.25 μg/kg/min.   There is an onset delay between the time
drug infusion begins and a perceptible increase in heart
rate is measured.   The onset delay is labelled 2 in Fig.
5.   Typically, the onset delay is approximately 1 minute
15 for arbutamine.   The onset time or time needed to achieve
steady state heart rate corresponding to a constant infu-
sion rate, is labelled by 3 on Fig. 5.   The offset delay,
the time during which heart rate continues at preexisting
levels after the infusion is stopped is labelled 4 on Fig.
20 5.   The offset delay is approximately the same as the
onset delay for arbutamine.   The offset region is that
after the offset delay, labelled 5 in Fig. 5.

        Pharmacodynamic analysis of arbutamine establishes
that there is a threshold level of action to achieve heart
25 rate response.   Typically, minimum infusion rate of 0.05
μg/kg/min. is necessary to observe a change in heart rate
sufficient to distinguish it from the noise level.

The Initialization Mode

        The initialization mode is shown at time T0 in Fig.
30 3, and represents the first stage in the drug phase.   At
the beginning of the ESA test, an effective threshold
level of drug must be established, and the onset delay
overcome.   In the preferred embodiment, an open loop 1
minute bolus of arbutamine is delivered at a constant
35 infusion rate of 0.1 μg/kg/min..   Based upon pharmaco-

22

dynamic analysis, the onset delay averaged 80 seconds,
with the range being from 25 seconds minimum to 125
seconds maximum. Generally, the onset and offset delay is
caused by the transport time from the point of drug admin-
5   istration to the heart and activation of the receptors.
The pharmacodynamic studies further show that the time
constant for onset to reach half maximum response value is
approximately 5 minutes, whereas the offset time to
decrease to half maximum is 7.5 minutes. The difference
10 between onset and offset half maximum times is believed to
be caused by a difference in association and disassocia-
tion of the drug with the beta agonist receptors of the
heart.

Control in LEVEL Mode (T1)

15   Fig. 3 shows the LEVEL mode at time T1. After the
initial bolus is delivered in the initialization mode
(T0), the control method closes the feedback loop on the
heart rate signal HRa and begins titrating the drug infu-
sion. Titration begins at the 0.1 μg/kg/min. delivery
20 rate   established   during   the   bolus   administration.
Initially, the control method target is set to plus 20 bpm
above baseline during LEVEL control. While this start-up
period is not essential, the following reasons weigh in
favor of the LEVEL mode prior to beginning higher rates of
25 drug infusion:

        (1) Because of patient-to-patient variability in the
        onset delay, some patients may not have responded to
        the drug during the bolus period. If the control
        method target were to continually increase before a
30   corresponding increase in heart rate occurred, an
        overly aggressive infusion profile could result.
        (2) Because of variations in patient-to-patient gain
        (differential heart rate gain per unit drug infusion)
        the response in heart rate to the initial bolus may
35   vary significantly. Providing a constant heart rate
        target during the LEVEL mode permits preliminary

23

estimate of the patient profile to be established.
The gain is preferably used in the control method for
later modes.

(3) The start-up period is selected to allow the
system sufficient time to show a response to drug
infusion. Because of the fixed target and the
conservative control during this period, the amount
of drug infused will be limited.

The Proportional-Integral Control Method

In the preferred embodiment, a proportional-integral
control method is used. The simple representation of the
proportional-integral formula to calculate the control
U(t) in discrete form is:

$$u(t) = kp * e(t) + ki * \sum_{1=0}^{\ell=t} e(1) \qquad (7)$$

where the tracking error is:

$$e(t) = trgt(t) - HRa(t) \qquad (8)$$

with trgt being the value of the desired trajectory and ki
and kp being the controller gains. The values for ki and
kp for various modes is listed in Table 1.

	Level Mode	Ramp Mode	Hold Mode	Target Mode
kp	4.0	4.0	2.0	2.0
ki	0.4	0.4	1.0	1.0

TABLE 1

Equations 7 and 8 may be combined and written
recursively as:

$$u(t) = u(t-1) + ki * e(t) + kp * (e(t) - e(t-1)) \qquad (9)$$

or:

$$u(t) = u(t-1) + k2 * e(t) - kp * e(t-1);$$
$$k2 = kp + ki \qquad (10)$$

24

Because of the input-output delay in the system, the correction terms with e(t) are added to an average of the infusion rates over the last minute (12 samples), giving the following formula for the average value of u:

$$\bar{u}(t-1:t-12) = \sum_{i=t-1}^{t-12} \alpha(i) * u(i) \tag{11}$$

The complete proportional-integral formula for the control method is given by:

$$u(t) = \bar{u}(t-1:t-12) - k2*(HRa(t)-trgt(t)) + \tag{12}$$

$$kp*(HRa(t-1)-trgt(t-1))$$

In the preferred embodiment, the weighing coefficient $\alpha(i)$ are selected as follows, to provide a stable but responsive infusion rate:

$$\alpha=\{0.1, 0.1, 0.1, 0.1, 0.1, 0.1, \frac{0.2}{3}, \frac{0.2}{3}, \frac{0.2}{3}, \frac{0.2}{3}, \frac{0.2}{3}, \frac{0.2}{3},\} \tag{13}$$

When in a mode in which the target is constant, such as in the LEVEL or HOLD mode, the proportional-integral rule may be written more simply as:

$$u(t) = \bar{u}(t-1:t-12) + kp*(HRa(t-1)-HRa(t)) +$$

$$ki*(trgt(t)-HRa(t)) \tag{14}$$

Transition from LEVEL to RAMP Mode (T2)

The transition from LEVEL to RAMP mode is shown at time T2 in Fig. 3. At this time, patients are prelimi-narily classified into one of three response categories. An "average" response is one in which the heart rate at the end of the start-up period (bolus plus LEVEL time, typically 4 minutes) has reached a value between 10 and 20 bpm above baseline heart rate. This "average" response is associated with an onset delay of 75 seconds or 15 time periods. A response is classified as "fast" if the patient reaches a 20 bpm increase over baseline during the start-up period. This is associated with an onset delay of 60 seconds or 12 time periods. Once a plus 20 bpm

25

increase in average heart rate is achieved, LEVEL mode
(T1) is exited and RAMP mode (T2) is entered, even if this
is before completion of the start-up period. A response
is classified as "slow" if there is less than a + 10 bpm
5   heart rate response at the end of the start-up period. A
"slow" response is associated with an onset delay of 90
seconds or 18 time periods. Because the heart rate
response is close to the noise LEVEL in a "slow" response,
optionally an alert is initiated. The onset delay esti-
10 mated in this mode is used for the remainder of the ESA
test, except in the case where a restart occurs at which
time the test for onset delay estimation is preferably
repeated.

        At the time of transition from LEVEL mode to RAMP
15 mode, the control method heart rate trajectory (desired
heart rate) is initialized at the then current average
heart rate HRa. This prevents a build-up of large
differences between the control method trajectory and
measured response. Further, the controller gains ki and
20 kp are selected for RAMP mode control from Table 1.

RAMP Mode Control

        In the preferred embodiment, the control method
attempts to match the rate of increase of heart rate to
the operator specified rate of increase. While a control
25 method based upon the absolute difference between the
target heart rate and the current heart rate could be
used, the possibility of excessive drug infusion rates is
less when the rate of increase in heart rate is the
control parameter. The proportional-integral formula
30 given above is utilized to calculate the infusion rate to
elicit a physiologic response to match the desired rate of
increase in heart rate. In the preferred embodiment, the
infusion rate calculations are performed every 15 seconds,
and the infusion rate adjusted accordingly.
35   There are two primary conditions which take the
control method out of the proportional-integral control

26

mode, those being the condition of saturation where the
heart rate response is not increasing sufficiently, and
over response where the heart rate is increasing too
rapidly.

5 Saturation

        In the case of saturation, it is has been observed
that the increase in heart rate no longer increases or
drops at higher infusion rates of arbutamine, typically
around 0.3 μg/kg/min. An increased desired heart rate
10 trajectory, combined with a saturation condition, could
result in a steep increase in infusion rates if the
proportional-integral control formula were to be strictly
followed. A saturation detection mechanism in the control
method detects saturation and alters the infusion rate,
15 and optionally triggers an alert or alarm condition.

        In the preferred embodiment, a peak detector tracks
the last maximum average heart rate and the current sample
index. If more than 30 seconds passes since the average
heart rate exceeded the last maximum heart rate, the
20 control method bypasses the proportional-integral formula.
In such a case, the infusion rate is incremented every 30
seconds by a small amount. The control method switches
back to the proportional-integral formula when the heart
rate peak detector finds a new average heart rate maximum.
25 In this way, rapid and unwanted increases in infusion
rates are avoided during periods of saturation. Optional-
ly, an alarm is sounded if an extended period of satura-
tion persists or a decrease of 10BPM of average heart rate
occurs.

30 Excessive Rate of Increase

        To determine if an excessive rate of increase in
heart rate is present, the control method periodically
calculates a value roughly equal to the rate of increase
of heart rate. In the preferred embodiment, an estimate
35 of the heart rate slope is calculated every 30 seconds.

27

At 30 second intervals, the trailing average of the
average heart rate over the last minute is calculated.
The rate of increase is taken to be twice the difference
between the new and old averages. If the slope exceeds
5 the limit value for the specified rate of increase, the
average infusion rate $\bar{u}(t-1:t-12)$ is scaled down according
to the following formula:

$$\text{scale} = \text{MAX(scalelimit, 1} - \text{(slope-limit)}/$$
$$\text{(2 * Desslope))}$$
10                        $$\text{scale} = \text{MIN(1.0, scale)}$$

where scalelimit is 0.97 (except the second time the
estimated slope exceeds the desired slope ("Desslope")
when scalelimit is 0.93), and "slope" is the actual rate
of increase. Limit is set with the following table:

15      $4 \leq$ Desslope ≤ 6 (LOW)   limit = 6
        $7 \leq$ Desslope ≤ 9 (MED)   limit = 9
        $10 \leq$ Desslope   (HIGH) limit = 12

Transition Into HOLD Mode and Operation in HOLD Mode

        The operator may demand a HOLD mode at any time.
20 Because of the relatively substantial onset and offset
delays for arbutamine, the drug already administered to
the patient will cause an effect even after the HOLD mode
command is received. In the preferred embodiment, it is
desired to minimize the overshoot of the heart rate above
25 the level for which a HOLD is desired.   A smooth
transition from RAMP to HOLD is desired.

        Broadly, upon receipt of a HOLD, the control method
decreases the drug infusion rate, often to a zero (0)
infusion rate, and subsequently resumes infusion up to a
30 rate necessary to sustain the desired heart rate level.
Typically, the rate of drug infusion necessary during the
RAMP mode will exceed the infusion rate necessary for a
HOLD at a given heart rate, thus ordinarily, the final
infusion rate is less than at the time HOLD was initiated.
35 Preferably, the maximum duration of the HOLD mode is 5

28

minutes, and the minimum HOLD LEVEL is + 20 bpm above
baseline.

Somewhat conflicting requirements are presented
between the RAMP mode and the HOLD mode. In the RAMP
5   mode, it is desired to increase at the selected rate of
increase, so as to most quickly achieve the desired heart
rate maximum. However, when a HOLD mode is initiated, it
is desired to minimize overshoot and to stabilize the
desired heart rate with minimal transient response. The
10 rule based system disclosed here provides for smooth
response.

In the preferred embodiment, the steps for transition
from the RAMP mode to the HOLD mode are as follows:

(1)   The controller gains ki and kp are set for the
15   HOLD mode as given in Table 1.

(2)   The operator selected rate of increase and the
infusion rate existing immediately prior to the HOLD
mode request are saved for use in transition out of
the HOLD mode.

20 (3)   The control method targets are set as follows:

If the HOLD mode is called during the RAMP
mode, the control mode is set at + 4 bpm above
the average heart rate HRa at the time HOLD
starts. Since the average heart rate HRa lags
25   the measured heart rate during the RAMP mode,
this addition adjusts the control method target
to an operator perceived level.

If the HOLD occurs during the start-up
mode, the control mode target is set to the
30   average heart rate HRa at the time the HOLD is
called.

(4)   The steady state infusion rate is initially
calculated as follows:

The estimated infusion rate ("E") is calcu-
35   lated based on estimated patient gain and HOLD
target level according to the following formula:

29

$$E = (\text{HOLD HR} - \text{baseline HR})/\text{Pgain}, \quad (15)$$

Where Pgain is a measure of the patient gain (see "Parameter Estimation", below).

If a RAMP mode was active for at least 2 minutes prior to the HOLD mode call, the pre-HOLD infusion rate (pHIR) is scaled relative to the estimated heart rate slope (described above) as set forth below:

$$(\text{slope}+\text{Desslope})/2 < 5 \quad \text{scale} = 0.9$$
$$5 \leq (\text{slope}+\text{Desslope})/2 < 9 \quad \text{scale} = 0.8$$
$$9 \leq (\text{slope}+\text{Desslope})/2 \quad \text{scale} = 0.6 \quad (16)$$

The average of this value with the previously estimated infusion rate is used as the steady-state estimate of the infusion rate (R):

$$R = [E-(\text{pHIR})*\text{scale}]/2 \quad (17)$$

This calculated infusion is bound by the maximum infusion rate then existing.

(5) If no saturation is detected and a RAMP mode precedes HOLD, a 1 minute open-loop control is used. In the preferred embodiment, the control method adjusts the infusion rate geometrically from 0 to the steady state level over a 1 minute interval according to the following rule:

$$\text{infusion} = \text{steady-state infusion} * (1.0-0.8^i);$$
$$i = 1,\ldots,12 \quad (18)$$

Because transitioning is from the RAMP mode, the built up momentum in the system, coupled with the sudden switch to HOLD mode, can result in some overshoot due to the offset delay inherent in the system. However, by following the above rules, the overshoot is minimized and the HOLD value achieved.

Transition Out of HOLD Mode (T4)

The transition point from the HOLD mode to the RAMP mode is shown at T4 in Fig. 3. To improve the resumption of heart rate increase to the RAMP mode, the initial

30

infusion rate is set to a different level. The following
steps are used:

    (1) The controller gains ki and kp are reset to the
RAMP mode levels of Table 1.

5   (2) The control method target is reset to the
present heart rate level HRa.

    (3) The initial infusion rate is set according to
the following rule:

Infusion Rate = 0.6 x (pre-HOLD infusion rate) +

10   0.4 x (end-HOLD infusion rate).

If the operator has decreased the desired heart rate
slope by more than 3 beats per minute per minute during
the HOLD, the prehold infusion factor is multiplied by 0.3
and the end HOLD factor is multiplied by 0.7.

15 Target Control (T5)

    As the heart rate approaches the target heart rate,
the control method acts to control drug administration in
an attempt to avoid overshooting the heart rate target.
This is typically effected by stopping infusion while the
20 heart rate is still below the target heart rate. Because
of the momentum in the system and the offset delay, the
heart rate will still increase after infusion is stopped.
This action may be taken according to the following
rules:

25   (1) Once the average heart rate equals the heart
          rate target minus 2 times the selected slope, the
          control system slope is automatically set to 4 bpm
          per minute.

      (2) The control system target is not permitted to
30   exceed the operator selected target. If the control
        system target equals the operator selected target
        heart rate, the target mode is entered and the
        controller gains ki and kp are set as provided in
        Table 1.

35 Alternatively, overshoot may be reduced by imposing a rate
of increase limit. For example, the maximum slope may be

set to 8BPM/min. when the average heart rate is within
range such as 20BPM) of the target heart rate.

Target Achieved (T6)

        Two separate criteria are used to determine whether
5   the operator selected heart rate target has been achieved.
Satisfaction of either of these criteria will terminate
drug infusion and initiate a transition to the post-drug
phase. The criteria are:

        (1) If a measured heart rate sample exceeds the
10   target heart rate and the next two heart rate
        measurements remain above the value (heart rate
        target minus 5 bpm), then the selected target is
        deemed to be achieved. The control system stops drug
        delivery.
15   (2) During the RAMP mode, the heart rate slope is
        calculated (described above) and as a result of this
        estimate, a "threshold to target" value is
        calculated. The following define the threshold for
        ranges of the average of the computed slope and the
20   desired slope ("AVERAGE"):
                if AVERAGE < 5, threshold = 5;
                if 5 ≤ AVERAGE < 9, threshold = 8; and
                if 9 ≤ AVERAGE, threshold =12.
When the average heart rate exceeds the value of heart
25 rate target minus threshold target value, drug delivery is
stopped and the heart rate target is deemed to have been
achieved.

        When in the HOLD mode, if either of these conditions
exists, infusion continues but an alert is triggered if
30 average heart rate is above the heart rate target. In
this way, a HOLD mode may be entered despite its close
proximity to the selected heart rate target.

32

Exit Drug Phase

In addition to achieving the heart rate target, a
transition from drug phase to post drug phase happens upon
any of the following events:

5   (1)   activation of an alarm,

           (2)   the operator issues an "interrupt" or "stop",

           (3)   the HOLD mode exceeds 5 minutes,

           (4)   the average heart rate is above the heart rate
                 target during the HOLD mode for 2 minutes.

10   During the post-drug phase, the infusion rate is set
to 0.

Restart to LEVEL Mode Control (T7)

It is possible to transition from the post-drug phase
to a second drug phase. This may occur if the operator

15 has designated such a protocol, or has made the requests
after the first protocol of ramp to target heart rate or
has remedied an alarm condition.

If the post-drug phase has been less than 30 seconds,
the control system merely resumes in the RAMP mode. In

20 the preferred embodiment, the control system is initial-
ized at the previously saved infusion rate, and the
control system heart rate target is set at the present
heart rate level HRa. No LEVEL mode control is activated.
However, if the post-drug phase lasts more than 30

25 seconds, a start-up period is inserted before the RAMP
mode is resumed. The start-up period is set for 3
minutes. Typically, the heart rate will be declining
during this post-drug phase. The restart period is used
to stop the downward decline in heart rate and to reverse

30 the decline toward an increasing rate. A constant target
is set at 10 bpm above the present average heart rate HRa
when restart was initiated. A "virtual baseline" is
formed since the heart rate is typically declining and,
owing to the onset delay, typically would decline a few

35 beats per minute towards the virtual baseline prior to

33

resuming an increase. The infusion rules for LEVEL mode
after restart are as follows:

      (1) If restart happens in the first 4 minutes of the
test, infusion is initialized at 0.1 μg/kg/min.;

5   (2) Otherwise, the infusion rate is calculated from
estimated patient gain and the control system target
heart rate;

      Infusion Rate = Target/Pgain.

      (3) Calculated infusion rate is limited to the value

10   of the previous highest infusion rate and by a rate
depending on the desired heart rate slope as
indicated in Table 2.

      $4 \leq$ Desslope ≤ 6 limit = 0.15 μg/kg/min

      $7 \leq$ Desslope ≤ 9 limit = 0.2 μg/kg/min

15      $10 \leq$ Desslope   limit = 0.3 μg/kg/min.

TABLE 2

Finally, all registers which kept track of various
variables, such as slope duration, slope estimation,
target threshold and maximum heart rate, from the prior

20 drug phase are reset.

RAMP Control After Restart (T8)

      The RAMP mode after restart is shown after time T8 in
Fig. 3. The transition to RAMP mode after the LEVEL mode
at restart is analogous to that described earlier for the

25 initial drug phase. The alert and alarm functions detect-
ing a lack of start-up responses are also reactivated.
The "virtual baseline" is taken to be the reference heart
rate for restart.

Parameter Estimation

30   An estimate of patient gain is used to calculate
infusion rates at the start of a HOLD mode and at the
restart. The patient gain estimate is calculated on-line
from a recursive least-squares parameter fit on the
pharmacodynamic model given by the following equations:

35      $HRa(t+1) + \alpha HRa(t) = \beta * u(t-n_k)$ (17)

34

This patient gain can be related to the estimated coefficients α and ß:

$$PGain = \frac{\beta}{1 + \alpha} \qquad (18)$$

5 Exemplary Results of Various Test Protocols

        Fig. 6 through Fig. 9 show various possible test protocol sequences. All figures show the average heart rate and dosage rate as a function of time, with the average heart rate being shown as a solid line and the
10 dose rate as the dotted line. The time is given in minutes, the heart rate in beats per minute and the infusion rate in micrograms per kilogram per minute.
        Fig. 6 shows a programmed single rise to heart rate target. The assumed patient is a 60 year old male. In
15 the preferred embodiment, the heart rate target is taken to the 136 beats per minute, calculated as .85x(220-60). The rate of increase of heart rate (slope) is set to a relatively low value of 4 bpm/min. The baseline heart rate value is established during the pre-drug phase (shown
20 as the time before time 0). The drug delivery phase begins at time t0, with the open-loop bolus injection shown as the relatively higher injection rate. In the preferred embodiment, after one minute, the LEVEL mode is entered for which a heart rate target of +20bpm is set.
25 Around time t=4 minutes, the heart rate has begun to rise and the RAMP mode is entered. As the heart rate rises towards the heart rate target of 136 bpm, the infusion rate also rises. At time t=19 minutes, the system determines that the average heart rate will reach the heart
30 rate target, and accordingly, terminates the drug infusion. After drug infusion stops, the heart rate reaches the target heart rate and begins its decline back towards the baseline heart rate.
        Fig. 7 shows a protocol having two heart rate rises
35 to two different heart rate targets. Again, it is assumed that the patient is a 60 year old male and accordingly the

35

heart rate target would be 136 bpm. Here, it is assumed
that the user adjusts the heart rate target to 115 bpm,
perhaps due to suspected coronary artery disease. As was
the case with the single rise to heart rate target proto-
5   col described in connection with Fig. 6, the first rise to
the heart rate target of 115 bpm follows a similar pattern
to time of 14 minutes. The heart rate continues to rise
briefly to reach the heart rate target and then begins to
decline. The second target of 136 bpm is then set and
10   drug delivery is restarted at t=16 minutes. The rate of
drug infusion at t=16 minutes is computed based upon the
rules described above. The heart rate decline stops and
the heart rate resumes its upward climb in a RAMP mode.
At time t=23 minutes, the method has determined that the
15   infusion is sufficient that the heart rate will achieve
the second heart rate target of 136 bpm, and accordingly
is terminated. The heart rate reaches the second target
and begins its downward decline to the baseline rate.

        Fig. 8 shows a protocol of a single rise to a target
20   heart rate, with the addition of a HOLD mode occurring at
time t=15 minutes. The initial bolus, LEVEL mode and RAMP
mode occur as described as above. When the HOLD is
selected at t=15 minutes, perhaps due to the suspected
indication of ischemia, the infusion rate immediately
25   drops significantly and then increases infusion rate to a
level estimated to provide maintenance of the heart rate
at the desired level. Once the HOLD is finished and the
RAMP restarted at t=19 minutes, the infusion rate is
increased according to the selection procedures described
30   previously. The RAMP mode and TARGET mode are then
completed, with the heart rate reaching the target of 136
bpm followed by subsequent decrease to the baseline.

        Fig. 9 shows protocol of a single rise, in which
ischemia is revealed. Again, the same assumptions are
35   made as in the case of Fig. 6, with the same infusion
rates and responses up until time approximately t=15
minutes. At that point, if the user gets an indication of

36

ischemia and desires to stop the test, pressing the STOP
button immediately terminates this infusion (shown at t=17
minutes). While there is a slight continued rise in heart
rate following termination of drug delivery, the heart
5   rate soon begins its decrease. In the preferred embodi-
ment, the patient is monitored for a relatively longer
period following drug termination in a case revealing
ischemia than in a case which does not indicate such a
condition.
10   It will be appreciated that any useful diagnostic
protocol may be used consistent with this invention. By
combining RAMPs of various slope and duration, in combina-
tion with various lengths of HOLD, virtually any achiev-
able desired heart rate may be specified as a function of
15   time. A RAMP need not be linear, but may be any desired
function of time.

Alerts & Alarms
          Numerous alert and alarm criteria may be optionally
implemented within the ESA device control program to
20   detect hazardous conditions or unexpected patient
responses to the drug. If an alarm is triggered during
drug delivery, infusion is immediately terminated. The
alarm condition remains in effect for a time period
sufficient to permit the condition to dissipate, but not
25   so long as to be annoying. In the preferred embodiment,
this time is set for 30 seconds. By such a choice, should
the operator elect to restart drug delivery, the 30 second
time will require the restart to begin with LEVEL mode
control. Alerts warn the operator of conditions that
30   should be corrected within a short time, but do not stop
drug delivery. The various alerts and alarms will be
described below.

No Start-Up Increase in Heart Rate
          It is necessary to verify that a patient is
35   responding to a drug both at the beginning of the test and

37

after a LEVEL mode restart. A "No Increase In Heart Rate"
alert is activated if:

> (1) At the beginning of a drug administration the
> average heart rate has not reached 10 bpm above
> baseline after 4 minutes (1 minute bolus plus 3
> minute start-up).

> (2) After a restart is initiated, if the heart rate
> average HRa is less than the heart rate average at
> the beginning of restart (after 3 minutes) the alert
> is activated.

The alert is cleared after 30 seconds. Three minutes
later, the "No Start-Up Increase In Heart Rate" alarm is
activated if the average heart rate maximum has not
reached 10 beats per minute above baseline in the case of
initial start-up or virtual baseline in the case of
restart.

Increasing IV Dose, No Increase in Heart Rate

These alerts and alarms detect saturation condition.
As previously described, the saturation condition occurs
when the average heart rate does not exceed the last
maximum average heart rate for a predetermined period of
time. Table 3 indicates the time in 5 second samples
between these two events which cause an alert or alarm.

	HRmax <= 40		HRmax <= 55 HRmax > 40	HRmax > 55
	Slope <=6	Slope > 6		
Alert (T1)	24	24	18	15
Alarm (PT1/PT3)	48	36	30	24

TABLE 3

Preferably, the alert is not active during HOLD mode,
start-up periods or prior to 1.5 minutes into the RAMP

38

mode.   The alarm is also triggered by either of the
following conditions:

    (1)   A 10 bpm drop in the average heart rate HRa from
    the previous maximum, or

5   (2)   Heart rate average HRa is 15 bpm below the
    desired target during HOLD mode.

Optionally, an additional alarm condition may be set
if the infusion rate is at maximum (typically 0.8 μg/kg/
min.) and the IV dose is increasing but heart rate is not
10 increasing.   Another optional alarm condition may be set
if the two alerts of 1) increasing IV dose, but no
increase in heart rate and 2) falling systolic blood
pressure occur at the same time.   These alerts and alarms
are preferably cleared 30 seconds after drug delivery is
15 stopped.

Irregular Heart Rate

During the drug delivery and post-drug phases, the
measured heart rate is compared to the averaged heart
rate.   If an absolute difference between the measured
20 heart rate and the average heart rate exceeds 20 bpm, the
average heart rate is stored.   If the next measured heart
rate again shows a difference of more than 20 bpm from the
now stored averaged heart rate, the irregular heart rate
alert is activated.   If the alert persists for 30 seconds,
25 the irregular heart rate alarm is activated.   This advises
the operator of short term irregularities in heart rate
signal, such as excessive outlier values, and detects
abnormal patient response to the drug.   The alert is
cleared whenever the difference between a new measured
30 heart rate and the stored heart rate average is less than
20 bpm or 30 seconds has passed in the case of post-drug
mode.

The Rapid Increase In Heart Rate Alert and Alarm

The rapid increase in heart rate alert is triggered
35 if the average heart rate HRa exceeds the control system

39

trajectory by 10 bpm. The alarm is activated if the alert condition persists for a period of time, such as 30 seconds or the average heart rate HRa exceeds the control system target by more than 20 bpm.

5 The Heart Rate Not Stable Alert and Alarm

The sum of the squares variance used in the pre-drug and drug phases, described above, is monitored to verify the quality of the feedback signal. An alert is triggered if the variance exceeds 100 bpm^2, corresponding to approxi-
10 mately to a "noise level" of 10 bpm. The heart rate not stable alarm is activated if the variance estimate exceeds 200 bpm^2, corresponding to a "noise level" of 14 bpm. The variance is not updated if (1) an irregular heart rate alert is active, (2) the ECG leads are removed or (3) an
15 uninterpretable heart rate has been observed, such as heart rate below 26 bpm.

Maximum IV Dose Alarm

This alarm is activated if the total amount of drug delivered over the complete period of test meets a speci-
20 fied amount. For arbutamine, a clinical limit of 10 $\mu g/kg$ is the upper limit. This alarm condition will not dis-appear until a new patient sequence is initiated. Optionally, the alarm flag may be cleared after 30 seconds to avoid undue operator irritation. However, further drug
25 delivery is not permitted, and if attempted, a "maximum I.V. dose" alarm is reactivated.

The Heart Rate Over Target During HOLD Mode Alert

If the heart rate exceeds the operator selected maximum heart rate during a HOLD mode, drug infusion is
30 not stopped, but the heart rate over target during HOLD alert is activated. This permits the operator to enter the HOLD mode at a level close to the maximum heart rate, but to avoid termination of drug delivery because of an erroneous heart rate target achieved due to overshoot when

40

entering the HOLD mode.   If the alert persists for 2
minutes, the target reached flag is set, which causes drug
infusion to stop and the post-drug phase to be entered.

Alarm From Combination of Alerts

5   Even when a single alert condition may not justify
terminating drug delivery, the existence of two or more
alerts may justify an alarm condition.   For example,
alerts relating to heart rate and to blood pressure, each
of which is merely on alert, may justify an alarm.   A
10 Falling Systolic Blood Pressure Alert plus a Heart Rate
Saturation Alert existing together cause an Alarm.

User Interface

        The user interface is preferably designed to permit
ease of operation.   Graphical representations of heart
15 rate, blood pressure and average heart rate are provided
to the user, as well as numeric indications of current
actual and average heart rate and blood pressure.   User
operated keys, optionally soft keys, permit modification
of heart rate trajectory during actual testing.   Further,
20 the interface permits rapid and easy initiation of a HOLD
or STOP command.

Description of the Preferred Hardware Embodiment

Hardware Specifics

        The external aspects of the ESA device have been
25 described in connection with Fig. 2.   Internally, the main
functional components may be grouped as follows: the data
acquisition functions, the display control functions and
the drug delivery control functions.   The data acquisition
functions serve to monitor the patient 15 (see Fig. 1) and
30 to provide the physiological parameter information 14 to
the ESA device 10.   The display functional aspects pro-
vide the output display 18 plus various other formats of
data output.   The drug delivery control functional system

41

controls the drug infusion rate based upon the drug
administration method described herein.

These functional aspects may be performed by any form
of hardware system which achieves the desired performance
5 and functional characteristics of this invention. Either
a single or multiple processor system may be used. The
system may be analog or digital, or a combination of both.

Fig. 10 shows a functional block diagram of the ESA
device. In the preferred embodiment. Separate micropro-
10 cessors are used for the various functional aspects of the
system.

In the block diagram of Fig. 10, the data acquisition
processor block 70 controls the data acquisition func-
tions. The display control processor block 80 controls
15 the display functions. The drug delivery processor block
90 determines the drug administration rate based upon the
rules provided above.

The data acquisition processor 70 provides the
interface between the patient and the overall ESA device.
20 In the preferred embodiment, the patient is monitored for
an ECG waveform through a 3 lead arrangement 72. An ECG
amplifier 74 functions to drive the selected ECG lead 72,
to electrically isolate the various ECG leads and to
amplify the ECG signal prior to input to the data acqui-
25 sition processor 70. Optionally, a non-invasive blood
pressure measurement system is provided. A non-invasive
blood pressure pump 76 inflates the cuff 78. Using any
desired technique, the systolic and diastolic pressures
are measured, and the pulse rate optionally determined.
30 The data from the ECG amplifier 74 and non-invasive blood
pressure cuff 78 are provided to the data acquisition
processor 70. The data acquisition processor 70 filters
the ECG signal, detects the QRS complex and calculates the
heart rate. This information is then transferred to the
35 display control processor 80. Optionally, electrical
isolation of the patient monitoring connections is
provided within the data acquisition processor 70.

42

The display control processor 80 serves the function of controlling the display and providing data transfer among the various processors. The display control processor 80 receives heart rate and blood pressure data from
5   the data acquisition processor 70. This data is provided to the drug delivery processor 90. The display control processor 80 receives as further input from the drug delivery processor 90 the ESA drug dosage rate plus alert and alarm information. The display control processor 80
10 stores data for printing and, optionally, may provide real time data output via a RS-232 data port. In one of its primary functions, the display control processor 80 controls and formats the graphic display 100 to provide visual displays for the operator. An ESA trend display
15 102 and labelling for the soft keys 104 are driven by the display control processor 80. The display control processor 80 drives an audiotone generator 82 to warn of alert and alarm conditions. Optionally, the display control processor 80 provides a system clock fed to the
20 data acquisition processor 70 and drug delivery processor 90 to synchronize operation. Finally, a system watch dog hardware circuit checks the display control processor 80 for proper operation.

The drug delivery processor 90 functions principally
25 to determine the drug infusion rate as determined by the control method system. The drug delivery processor 90 receives alerts and alarms, plus heart rate and blood pressure data from the display control processor 80, plus inputs from the hard key pad 110. Additionally, the drug
30 delivery processor 90 receives a response signal from the IV drug delivery source 120. Patient specific data is input from the hard key pad 110, which is optionally transmitted to the display control processor 80 for display. The hard key pad 110 provides the input for initial
35 heart rate target and heart rate slope, patient specific data (such as weight and age) plus protocol adjustments such as changes to heart rate target, heart rate slope or

43

the HOLD mode.   The drug delivery processor 90 monitors
the IV drug delivery pump 122 for alerts and verifies dose
rate commands.   The drug delivery processor 90 drives a
second audiotone generator 92 to indicate one of alerts
5 and alarm conditions.   The drug delivery processor 90 also
controls the system status LEDs 106.   A second watchdog
hardware circuit 94 checks the drug delivery processor for
proper operation.

All of the rules described above are stored in memory
10 for use by the various processors.   Any form of memory,
whether solid state, magnetic or otherwise, may be used to
store the program and rules.

The IV drug delivery source 120 may consist of any
drug delivery apparatus consistent with the invention.   In
15 one embodiment, an intravenous drug delivery system is
used.   A IV syringe pump 122 controls drug administration
rate by controlling motion of a syringe plunger.   Prefer-
ably, the syringe is contained under an interlocked cover.
The IV extension set connects the syringe to venipuncture
20 device, not shown.   In operation, the IV drug delivery
source 120 provides the drug delivery processor 90 with
infusion rate information.

In an alternative embodiment, a transdermal drug
delivery system may be utilized.   The details of a
25 particularly useful transdermal drug delivery system are
described in Apparatus and Method for Iontophoretic
Transfer, Serial No. 07/471,296, Filed January 26, 1990,
incorporated herein.   Preferably, the drug delivery pro-
cessor 90 would provide the transdermal dose commands to
30 the transdermal drug delivery current source 130.   The
current source 130 then drives the drug electrode 132 with
the indifferent electrode 134 providing the completion to
the current circuit.   Optionally, voltage and current
confirmation may be provided from the transdermal drug
35 delivery device to the drug delivery processor 90.
Preferably, the transdermal drug delivery current course
130 limits the current and voltage to safe levels, such as

44

voltage less than 100 volts dc max and current less than
5 milliamps.

    Though the invention has been described with respect
to a specific preferred embodiment, many variations and
5 modifications will immediately become apparent to those
skilled in the art.   It is therefore the invention that
the appended claims be interpreted as broadly as possible
in view of the prior art to include all such variations
and modifications.

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Claims

    1.   A method for cardiac diagnosis using an exercise simulating agent in a closed-loop drug delivery system which controls the patient heart rate comprising the steps

5 of:

    a)   defining a protocol, the protocol including at least a target heart rate and a plan to achieve the target heart rate,

    b)   begin drug delivery to execute the protocol, and

10   c)   modifying the protocol after drug delivery begins.

    2.   The method for cardiac diagnosis of claim 1 where in step c the protocol is modified by varying the target heart rate.

15   3.   The method for cardiac diagnosis of claim 2 where in step c the protocol is modified by varying the plan.

    4.   The method for cardiac diagnosis of claim 1 where in step a the protocol further includes defining the

20 desired rate of increase in patient heart rate during closed-loop delivery.

    5.   The method of claim 4 where in step c the protocol is modified by varying the desired rate of increase in the patient's heart rate.

25   6.   A method for control of a patient physiological variable in a closed-loop drug delivery system comprising the steps of:

    a)   defining a protocol including a target value of the patient physiological variable and a plan to achieve

30 the target value of the patient physiological variable, and an acceptable zone of deviation from the plan,

46

    b)   initiate drug delivery under a control system defined by a first set of rules,

    c)   monitor the patient physiological variable, and

    d)   change from the first set of rules to alternate rules if the patient physiological variable is outside the acceptable zone of deviation from the plan.

7.   The method of claim 6 where in the patient physiological variable is the heart rate.

8.   The method of claim 6 or 7 where in step d the alternate rules include an alert or alarm condition.

9.   The method of claim 6 or 7 where in step d the alternate rule includes open-loop administration of the drug.

10.   The method of claim 6 or 7 where the alternate rule includes a proportional-integral control.

11.   The method of claim 6 or 7 where in step d the alternate rule includes a proportional-integral-derivative control.

12.   The method of claim 6 or 7 where in step a the acceptable zone of deviation from plan includes definition of a maximum acceptable value for the patient physiological variable.

13.   The method of claim 6 or 7 where in step a the acceptable zone of deviation from plan includes a maximum acceptable rate of increase in the patient physiological variable.

14.   The method of claim 6 or 7 where in step b the control system is a proportional-integral control system.

47

15.   The method of claim 6 or 7 where in step b the control system is a proportional-integral-derivative control system.

16.   A control system for closed-loop drug delivery
5 for diagnostic purposes comprising the steps of:
      a)   administering the drug,
      b)   monitoring the patient response to the adminis-tered drug,
      c)   determining the individual patient response to
10 the administered drug, and
      d)   conduct diagnostic procedure with the closed-loop controller utilizing the individual patient response information.

17.   The method of claim 16 where the individual
15 patient response information includes patient gain.

18. The method of claim 16 where in the individual patient response includes an estimation of the time constant for drug response for the patient.

19.   The control system of claim 16 where the indi-
20 vidual patient response information includes the onset delay for the drug.

20.   The method of claim 16 where in the drug is an exercise simulation agent used for cardiac diagnosis.

21.   A method for medical diagnosis using closed-loop
25 drug delivery and a variation of a patient physiological variable comprising the steps of:
      a)   specifying a desired rate of increase in the patient physiological variable,
      b)   administering a drug which causes variation in
30 the patient's physiological variable,
      c)   monitoring the patient physiological variable,

48

d)   determining the rate of change in the patient
physiological variable, and

e)   controlling the drug delivery in the closed-loop
system to achieve the determined rate of change of the
5   patient physiological, variable equal to the desired rate
of change in the patient physiological variable.

22.   The method of claim 21 where in the patient
physiological variable is heart rate.

23.   The method of claim 21 where in the desired rate
10   of change in the patient physiological variable is a
positive number.

24.   A method for closed-loop drug delivery for
cardiac diagnosis using an exercising simulating agent
drug comprising the steps of:
15   a)   specifying a protocol, the protocol including a
target heart rate,

b)   establishing a baseline heart rate,

c)   determining the individual patient response to
the drug,
20   d)   monitoring the heart rate,

e)   administering the drug based upon predefined
rules, the monitored heart rate and the individual patient
response, and

f)   output the results to the operator.

25   25.   The method of claim 24 where in the protocol
specifies the desired rate of increase in the heart rate.

26.   The method of claim 24 where in the protocol
specifies the time of hold at the target heart rate.

27.   The method of claim 24 where in the protocol
30   specifies patient specific information.

49

28. The method of claim 24 further including the step of establishing a baseline for the blood pressure.

29. The method of claim 24 where in step c where in the individual patient response is determined in response
5   to an open loop administration of the drug.

30. The method of claim 24 where in the step c the determination of individual patient response includes the patient gain.

31. The method of claim 24 where in step c the
10 determination of individual patient response includes determination of the time constants for the patient to the drug.

32. The method of claim 24 where in the monitored heart rate is average prior to use in step e.

15 33. The method of claim 24 further including the step of monitoring the patient blood pressure.

34. The method of claim 24 further including the step of monitoring for saturation.

35. The method of claim 24 where in step e the rules
20 include control for a ramp mode.

36. The method of claim 24 where in step e the rules include an initialization mode.

37. The method of claim 24 where in step e the rules include a level mode.

25 38. The method of claim 24 where in step e the rules include a proportional-integral control method.

50

39. The method of claim 24 where in step f the output includes a trend plot.

40. The method of claim 24 where in step f the output includes real time data provided to the operator.

5   41. The method of claim 24 further including the step of issuing alerts or alarms.

42. The method of claim 24 further including the step of filtering the monitored heart rate.

43. The method of claim 24 where in step e the rules
10 respond to receipt of a hold command.

44. A method for a achieving a RAMP mode in a closed-loop drug delivery system where the rate of drug delivery affects a physiological parameter, comprising the steps of defining a desired rate of increase in the
15 physiologic parameter, and administering the drug at a rate so as to achieve a rate of increase in the physiologic parameter equal to the desired rate.

45. A method of claim 44 where in the physiologic parameter is the heart rate.

20   46. A method for achieving a HOLD mode in a closed-loop drug delivery system where the rate of drug delivery affects a physiologic parameter, comprising the steps of:
       receipt of the HOLD condition,
       initial reduction in the rate of drug delivery,
25   subsequent increase in the rate of drug delivery, such that at the end of the increase, the rate of drug delivery results in maintenance of the physiologic parameter at the desired value.

51

47. The method of claim 46 where in the initial reduction in the rate of drug delivery is to a zero rate of infusion.

48. The method of claim 46 in which the increase in
5 the rate of drug is done exponentially from the rate after reduction to the rate which results in maintenance of the physiologic parameter at the desired value.

49. A filtering method for use in a closed-loop drug delivery system, where drug is administered and the
10 physiologic parameter of the patient is monitored and used as the input to a closed-loop control system, the method comprising the steps of:
        clipping outliers based upon preset limits, and
        low pass filtering the physiologic parameter.

15   50. The filtering method of claim 50 where the patient's heart rate is the monitored physiologic parameter.

51. The filtering method of claim 50 where in outliers in the range outside of +6 and -8 beats per
20 minute are clipped.

52. The filtering method of claim 50 where in a first fraction of the current measured value is combined with a second fraction of a value based upon previously measured values.

25   53. A method for detecting saturation in cardiac response to an ESA drug comprising the steps of:
        sampling a signal indicative of heart rate,
        monitoring for peak heart rate,
        determining the length of time since the last heart
30 rate peak was detected,

52

generating a signal indicative of saturation when the
length of time since the last heart rate peak was detected
exceeds a pre-set time limit.

54.   The method of claim 28 where in the preset time
5 limit is 30 seconds.

55.   A filtering method for use in a closed-loop drug
delivery system, where drug is administered and a physio-
logical parameter of the patient is monitored and used as
the input to a closed-loop control system, when in a RAMP
10 mode, the method comprising the steps of:
     measuring the physiologic parameter of the patient,
     determining the slope of the physiologic parameter as
a function of time,
     comparing the computed slope with a threshold value,
15 and
     generating a signal indicative of saturation condi-
tion if the measured slope is less than the threshold
slope.

56.   A method for determining an excessive rate of
20 increase in a cardiac diagnostic procedure comprising the
steps of:
     calculating a value indicative of the heart rate at
a first time,
     calculating a value indicative of the heart rate at
25 a second time,
     generating the difference between the two calculated
values,
     comparing the difference with a preset value, and
     generating a signal indicative of an excessive rate
30 of increase if the difference meets or exceeds the preset
value.

57.   In a closed-loop drug delivery method, where a
physiologic parameter is controlled for diagnostic

53

purposes based upon drug administration, the improvement
comprising the addition of a hold mode which permits the
an operator to specify a hold mode to maintain the value
of the physiologic parameter.

5   58. The method of claim 32 where in the physiologic
parameter is the heart rate.

         59. In a closed-loop drug delivery system adminis-
tering an exercising simulating agent to elicit stress,
where the patient heart rate is monitored in response to
10 the administration of the drug, the improvement comprising
monitoring the patient for a saturation level of the drug.

         60. A method for determining when a target heart
rate has been achieved in a closed-loop drug delivery
system using an excessive simulating agent, comprising the
15 steps of:
         monitor the patient heart rate,
         determine the patient heart rate slope,
         generate a threshold to target valve based in part on
the heart rate slope, and
20   terminate drug delivery when the patient heart rate
exceeds the target heart rate minus the threshold to
target value.

         61. The method for determining when a target heart
rate has been achieved in claim 60 where the threshold to
25 target value is generated based upon the heart rate slope
and the desired slope.

         62. The method for determining when a target heart
rate has been achieved of claim 61 where the threshold to
target value is generated based upon the average of the
30 heart rate slope and the desired slope.

54

63. A method for determining an alarm condition during a cardiac diagnostic procedure utilizing more than one alert condition, comprising the steps of:

monitoring for a first alert condition,

5   monitoring for a second alert condition, and

generating an alarm condition if the two alert conditions are coincident.

64. The method of claim 63 where the first alert condition is falling systolic blood pressure alert and the

10   second alert condition is a heart rate saturation alert.

65. A drug delivery system for closed-loop adminis-tration of an exercise simulation agent for purposes of inducing cardiac stress in a patient comprising:

means for acquiring data from the patient,

15   including the patient heart rate,

means for controlling the drug delivery based upon the data from the patient and predefined rules,

a memory for storing the predefined rules,

a drug delivery system, and

20   means for interfacing with an operator of the system.

66. The drug delivery system of claim 65 where the drug delivery system includes a transdermal drug delivery electrode.

67. The drug delivery system of claim 65 where the

25   drug delivery system includes an intravenous delivery system.

68. The drug delivery system of claim 65 where the means for acquiring data from the patient further acquires blood pressure data.

69. The drug delivery system of claim 65 where the means for interfacing with an operator of the system includes a graphic display.

70. The drug delivery system of claim 65 where the
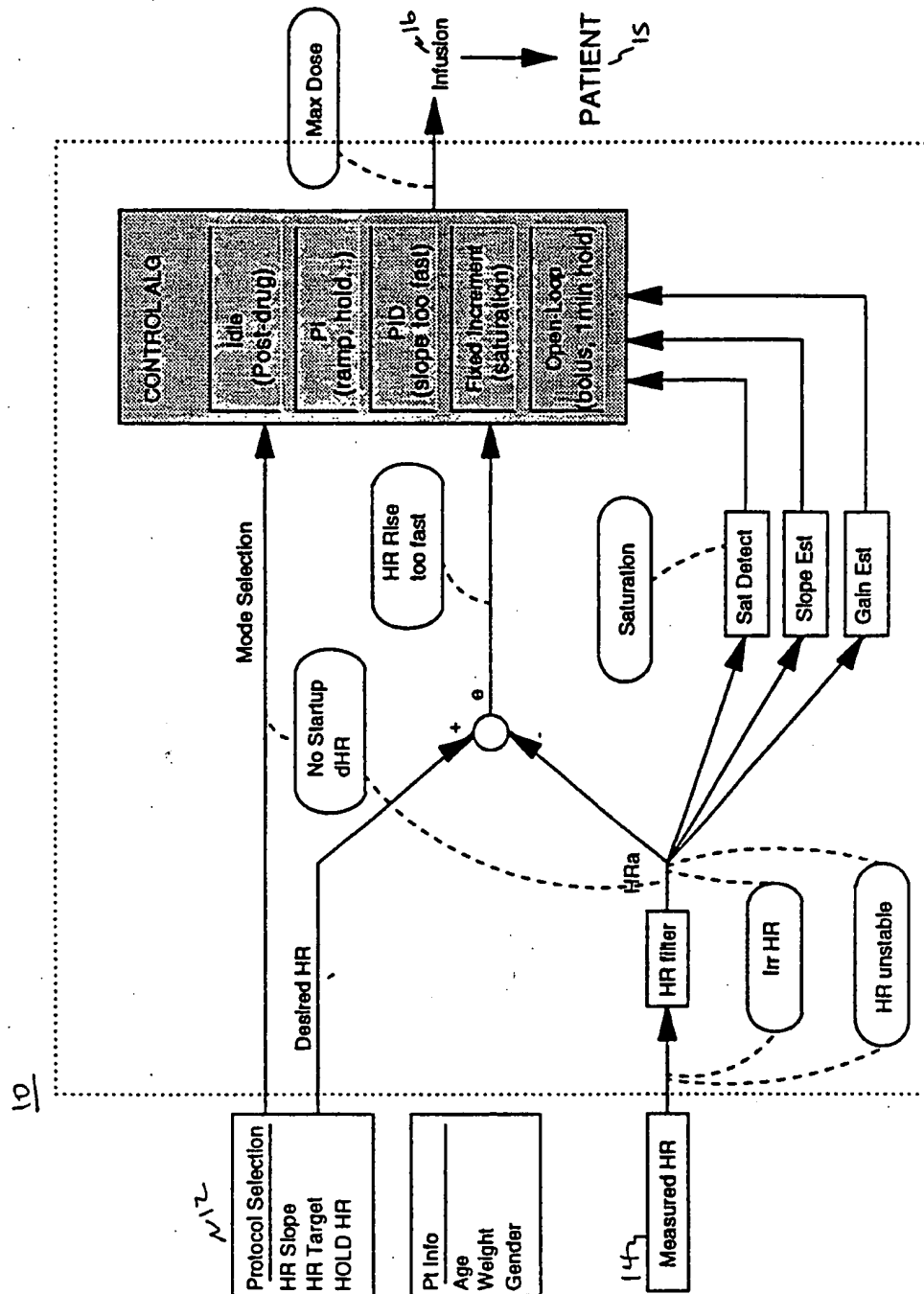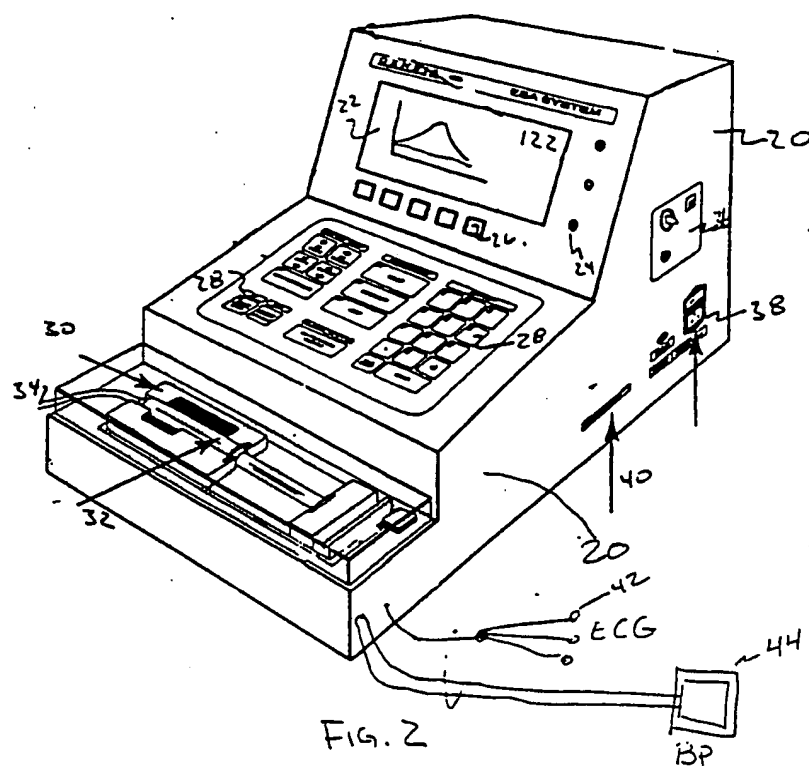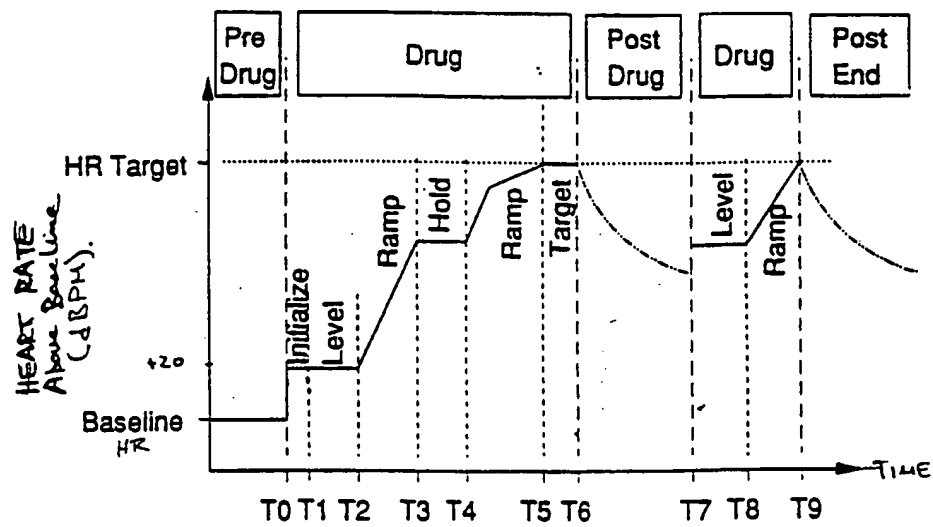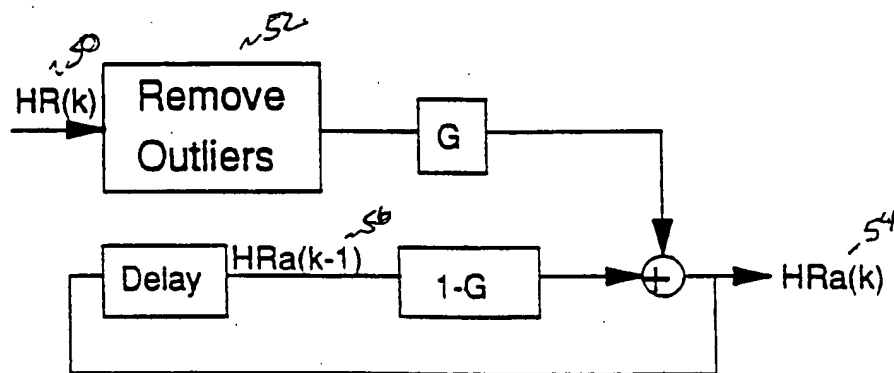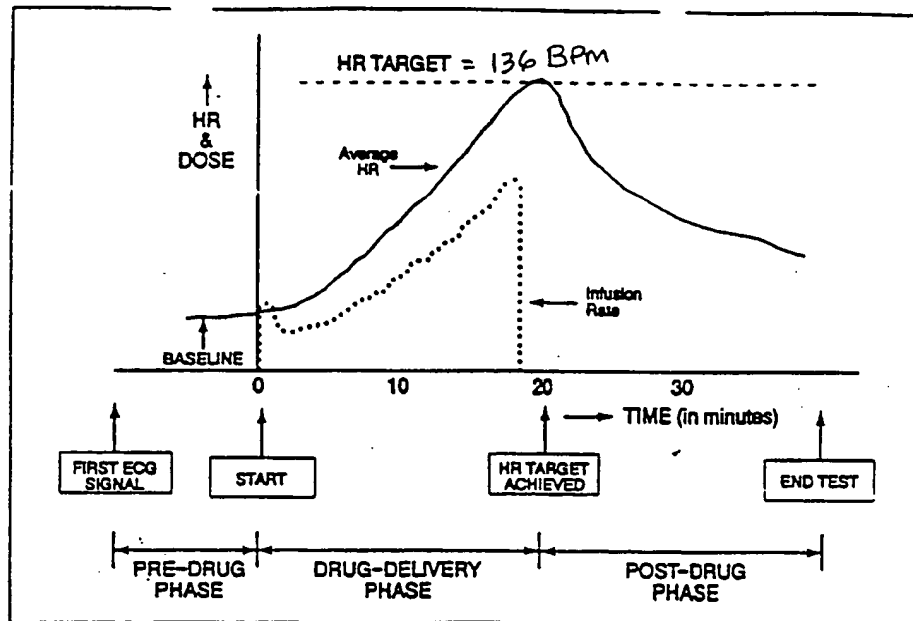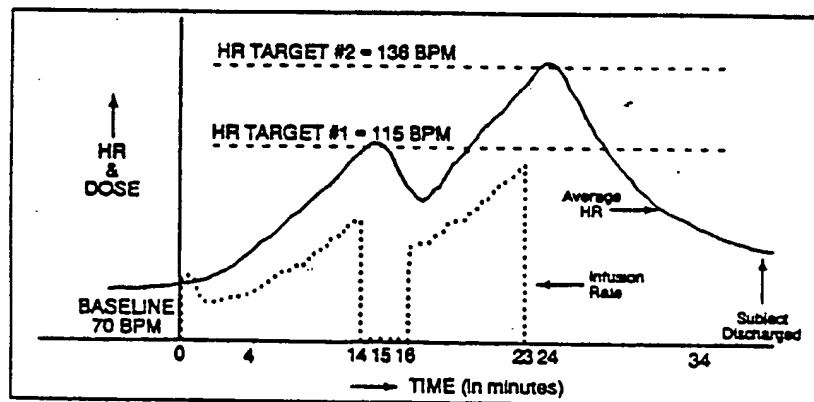5   means for interfacing with an operator of the system includes a audio generator.

Fig. 1

FIG. 2

FIG.3

FIG 4

FIG. 5.

Fig. 6

Fig. 7

Fig. 8

Fig. 9

ESA SYSTEM - DEVICE FUNCTIONAL BLOCK DIAGRAM